REMARKS

The inadvertent failure to delete "such as Boc" in claim 15 has been remedied above. In view of this change, it is respectfully submitted that the rejection under 35 U.S.C. § 112 can now be withdrawn.

Claims 14-16, 18, 20-22, and 26-30 under 35 U.S.C. § 103(a) over Funk in view of O'Neill, Hubbs and Veber; Claims 14-26 have been rejected under 35 U.S.C. § 103(a) over Funk in view of O'Neill, Hubbs and Veber and in further view of Gefter; and Claim 26 has been rejected under 35 U.S.C. § 103 over Funk in view of O'Neill. All of these rejections are respectfully traversed.

With one exception, all of the rejected claims relate to a process. The exception is claim 26 which relates to a tripeptide. We will first consider the process claims.

The process claims are all are dependent, directly or indirectly, on claim 14. Claim 14 recites a three-step process for making a tripeptide compound X-D-2Nal-D-4ClPhe-D-3Pal-OH in which X is Boc or Ac. In this tripeptide, the amino terminus is protected by Boc or Ac and the carboxyl terminus is not protected.

In the first step, Boc-D-4ClPhe-OH is reacted with HONSu to form a compound VII, Boc-D-4ClPhe-OSu. In the second step, that compound is reacted with H-D-3Pal-OH to form compound VIII, Boc-D-4ClPhe-D-3Pal-OH, and in the third step, VIII is then reacted with BOC-D-2Nal-OSu to form compound IX (compound X where "X" is Boc). Optionally, compound IX is reacted with acetic acid to replace the Boc with Ac. The cited references do not teach or suggest the claimed process.

An important aspect of the present invention concerns ester protection. The process of the invention is a synthesis without ester protection in contrast to the prior art, such as Funk, which always employs ester protection. Note the VIII in the claims is not carboxy protected. In the present invention, the amino terminus protected peptide is pre-activated in the first step with HONSu as an activating agent before H-D-3Pal-OH is employed, thereby avoiding activation of the carboxyl group of this additional reactant. The generation of this activated peptide (VII) is important because many activated carboxylic acid derivatives are capable of cross-activation of another carboxylic acid. In the invention, the expected cross-activation does not occur.

The Office Action asserts that the relevant method steps are found in Funk and makes reference to scheme III which starts at the top of column 11. That process starts by coupling an amino protected D-4ClPhe-OH with the hydrochloric salt of D-3Pal-O-P[4] to make an amino and carboxy protected P1-D-2Nal-D-4ClPhe-D-3Pal-O-P4. There is no teaching or suggestion anywhere in scheme III (or elsewhere in Funk) of activating the amino protected 4-ClPhe-OH with HONSu and indeed, Examiner acknowledged that fact in a previous Office Action.

In an attempt to avoid this deficiency, the Office Action asserts that "HONSu is well-known to be used in coupling, and thus one would readily use any coupling agent to form the amide bond, and one would use any protecting group, as many are well known and widely used in peptide synthesis." The only potential support for this assertion is the quotation from column 10 of Hugs to the effect that "the condensation reaction of the two fragments can be accomplished [by] treatment of the two peptide fragments with condensation reagents...and an activating agent [such as HONSu]." This teaching might have been pertinent if what was being claimed is the condensation of two peptide

fragments with condensation reagent(s) in the presence of HONSu, but that is not what is claimed. Claim 14, step (a). calls for reacting Boc-D-4ClPhe-OH with HONSu to form Boc-D-4ClPhe-OSu. Whether one skilled in the art would have used HONSu as an activating agent or to inhibit racemization during the coupling of two fragments does not appear to have any relevance to the process actually claimed herein. Further, the Examiner will note that the very first step in Funk synthesis III involves protecting the carboxy terminus which remains protected throughout the balance of the procedure. This is in contrast to the claimed process where the carboxy terminus is unprotected.

Beyond the foregoing, the claimed synthesis in which the carboxy terminus is unprotected gives rise to an increased yield and this is both surprising, unexpected and unpredictable based on the prior art.

The following table compares the instant process and that of Funk where Q is THF-Gly starting from the same material:

Acetate by the method of the invention starting from Boc-D-4ClPhe-OH	Yield, %	2-R,S-THF-Gly analogue by to the method of US 5,710,246 starting from Boc-D-4ClPhe-OH	Yield, %
Boc-D-4ClPhe-OSu	85	Boc-D-4ClPhe-D-3-Pal-O-Me	80
Boc-D-4ClPhe-D-3Pal-OH	80	Boc-D-2Nal-D-4ClPhe-D-3Pal-OMe	80
Boc-D-2Nal-D-4ClPhe-D-3Pal-OH	90	2R,S-THF-Gly-D-2Nal-D-4ClPhe-D-3Pal-O-Me	40

Ac-D-2Nal-D-4ClPhe-D-3Pal-OH	70*	2R,S-THF-Gly-D-2Nal-D-4ClPhe-D-3Pal-OH	50
Total yield:	47.6%	Total yield:	12.8%

*In respect of Boc-D-4ClPhe-D-3Pal-OH

There is no reason to assume that the yield would significantly vary when Q is Ac (making the final product the same in both columns). One skilled in the art would not have expected the superiority of the claimed method. There is no way of predicting an increased yield by avoiding carboxy protection.

The current rejection also asserts that it would have be obvious at the time the invention was made to have made the Boc protected peptide with the expectation that the compound would function as a N-acetyl counterpart in the synthesis of LHRH analogs. The basis for this is said to be an expectation that the Boc protected peptide would "function similarly". It is respectfully submitted that this conclusion is not well taken for the following reasons.

First it appears that the assertion that the Ac and Boc "functions similarly" is based on merely characterizing them as protecting groups while at the same time, ignoring fundamental differences between them. When a product of a condensation is going to be reacted in order to couple other entities, such as occurs in the synthesis of LHRH analogs, the protecting groups must be removable selectively. It is here that Boc and acetyl groups have very different properties. The Boc can function as a temporary protective group while the Ac does not. The acetyl group in Funk cannot be removed and therefore a simple further elongation of the peptide is not possible. In this connection, the examiner

will note that in Funk scheme 1, the intermediate (III) contains an acetyl group as moiety Q (col. 7, lines 18-19) and this moiety is carried forward into the final product (VI).

Another important difference is that condensation of an Ac amino acid causes epimerization (racemization). Thus, if an Ac-D-2-Nal-OH is condensed with H-D-4ClPhe-D-3Pal-OR (R=H, alkyl), a major amount of Ac-L-2Nal-D-4ClPhe-D-3-Pal-OR is produced.

It is clear from the foregoing that the Ac and Boc do not "function similarly" and therefore one skilled in the art would not be motivated to substitute one for the other in any and all circumstances.

Funk teaches that compounds used a pre-intermediate for the preparation of compound III are always esterified at the C-terminus. In compound III, the N-terminus is Q which is defined to be either Ac or THF-Gly. If one skilled in the art wanted to make a compound where Q is Ac, then there is no reason to employ a Boc protected intermediate rather than an Ac intermediate (even if one ignores the ester at the other terminus) because the 2 groups function very differently and why use Boc when Ac is ultimately desired? . Why one skilled in the art would ever be motivated to employ a Boc protected group when it is desired that Q be THF-Gly is also not apparent. All of the N-terminus protected compounds III and there is no reason to make the N-protected C-non-protected tripeptide of claim 26. There is clearly no justification or motivation for making the tripeptide of the instant claim 26. Whatever justifications may be intoned after reading the present application cannot substitute for a prospective justification as of the filing date of this application without using the application as a template.

In the context of the rejection against the pending process claims, O'Neill has apparently been relied upon solely to show particular nitrogen protecting groups. It does not teach or suggest that a process in which the carboxy terminus does not need protection even be attempted. Veber has been cited to similarly show that certain hydroxy protecting groups exist but again there is no teaching or suggestion of a process in which a synthesis is not carried out without ester protection. The significance of Hubbs has been considered above. The selection on certain group and reagents is not obvious unless done with the use of the application as a template, and that is not permissible.

Additional reliance on Gefter does not cure any of the deficiencies of the four reference combination and therefore cannot serve to render any of these process claims obvious. It has no relevance to the broadest process claim, claim 14.

While the foregoing discussion has considered the process claims primarily, it has also provided a variety of reasons why the product claim 26 is patentable over the art being applied against it. For the reasons stated, the making of the product of claim 26 is clearly not rendered obvious by the prior art.

Further, the conversion yield in Funk of the ester to the non-ester when Q is THF-Gly is 50% and a similar yield would be expected when Q was Ac. In the invention, the compound of claim 26 permits the same Ac product to be obtained in a yield of 70%. This is surprising and unexpected. It is clearly unpredictable. Nothing in the prior art teaches or suggests or allows one to have a reasonable expectation that the tripeptide of the instant claim 26 could contribute to this unexpected superiority.

In light of all of the foregoing, it is respectfully submitted that claim 26 is allowable.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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